IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TALECRIS BIOTHERAPEUTICS, INC. and BAYER HEALTHCARE LLC, Plaintiffs, v. BAXTER INTERNATIONAL INC. and BAXTER HEALTHCARE CORPORATION, Defendants.	C. A. No. 05-349-GMS JURY TRIAL DEMANDED **PUBLIC VERSION**
BAXTER HEALTHCARE CORPORATION, Counterclaimant, v. TALECRIS BIOTHERAPEUTICS, INC. and BAYER HEALTHCARE LLC, Counterdefendants.	

CORRECTED DECLARATION OF BRIAN T. CLARKE IN SUPPORT OF DEFENDANT BAXTER INTERNATIONAL INC. AND DEFENDANT/COUNTERCLAIMANT BAXTER HEALTHCARE CORPORATION'S MOTION FOR LEAVE TO FILE AMENDED ANSWER AND COUNTERCLAIM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TALECRIS BIOTHERAPEUTICS, INC. and BAYER HEALTHCARE LLC, Plaintiffs, v. BAXTER INTERNATIONAL INC. and BAXTER HEALTHCARE CORPORATION, Defendants.	Civil Action No.: 05-349-GMS Jury Trial Demanded **PUBLIC VERSION**
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I, Brian T. Clarke, declare:

1. I am an associate at the law firm of Townsend and Townsend and Crew LLP and one of the counsel of record for Defendant Baxter International Inc. and Defendant/Counterclaimant Baxter Healthcare Corporation (collectively "Baxter"). I make this declaration of my personal knowledge.

2. I am personally aware that Anne M. Rogaski (also counsel of record in this case) spoke with Plaintiffs' counsel pursuant to D. Del. L. R. 7.1.1, Mr. Jeffery B. Bove, in the afternoon of October 27, 2006 to inform him that Baxter was seeking the Plaintiffs' stipulation to file an Amended Answer and Counterclaim to add inequitable

conduct as a defense and a related counterclaim. Ms. Rogaski advised Mr. Bove that Susan Spaeth (also counsel of record in this case) would send him a copy of the proposed Amended Answer and Counterclaim on Monday, October 30, 2006 for his review, which Ms. Spaeth did in-fact do. I am personally aware that in a subsequent meet and confer with Ms. Rogaski counsel for Plaintiff, Mr. Bove, specifically indicated that Plaintiffs would not stipulate to Baxter filing an Amended Answer and Counterclaim.

3. I am personally aware that Plaintiffs' counsel represented the attorneys who prosecuted the '191 Patent in connection with their depositions in this case.

4. A true and correct copy of the patent-in-suit, U.S. Patent Number 6,686,191 (Alonso), is attached hereto as Exhibit 1.

5. A true and correct copy of the Examiner's Answer Before the Board of Patent Appeals and Interferences is attached hereto as Exhibit 2.

6. A true and correct copy of the Final Office Action, dated May 14, 1996, is attached hereto as Exhibit 3.

7. A true and correct copy of the Applicant's Appeal Brief to the Board of Patent Appeals and Interferences is attached hereto as Exhibit 4.

8. A true and correct copy of the Decision on Appeal in *Ex parte William R. Alonso* is attached hereto as Exhibit 5.

9. A true and correct copy of the Applicant's Response to the First Office Action, dated May 9, 1996, is attached hereto as Exhibit 6.

10. A true and correct copy of the Applicant's Amendment After the Final Office Action, dated November 18, 1996, is attached hereto as Exhibit 7.

11. A true and correct copy of TAL038422 is attached hereto as Exhibit 8.

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12. A true and correct copy of TAL018558 is attached hereto as Exhibit 9.

13. A true and correct copy of TAL018537-TAL018564 is attached hereto as Exhibit 10.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 22nd day of December, 2006, in Palo Alto, California.

Brian T. Clarke

Public Version: January 3, 2007

EXHIBIT 1

US006686191B1

(12) **United States Patent**
Alonso

(10) **Patent No.: US 6,686,191 B1**
(45) **Date of Patent: Feb. 3, 2004**

(54) **PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN**

(75) Inventor: **William R. Alonso**, Cary, NC (US)

(73) Assignee: **Bayer HealthCare LLC**, Tarrytown, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1772 days.

(21) Appl. No.: **08/532,211**

(22) Filed: **Sep. 22, 1995**

(51) Int. Cl.[7] C12N 7/04; A61K 39/395; A61K 39/40; A61K 39/42

(52) U.S. Cl. 435/236; 424/176.1; 424/177.1; 424/130.1

(58) Field of Search 530/390.1, 390.5, 530/386, 387.1; 424/176.1, 177.1, 130.1; 435/236

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,396,608 A * 8/1983 Troold
4,540,573 A * 9/1985 Neurath et al.
4,762,714 A * 8/1988 Mitra et al.

OTHER PUBLICATIONS

Joy Yang, Y.H. et al. "Antibody Fc functional activity of intravenous immunoglobulin preparations treated with solvent–detergent for virus inactivation" Vox Sang, vol. 67, pp. 337–344, May 17, 1994).*

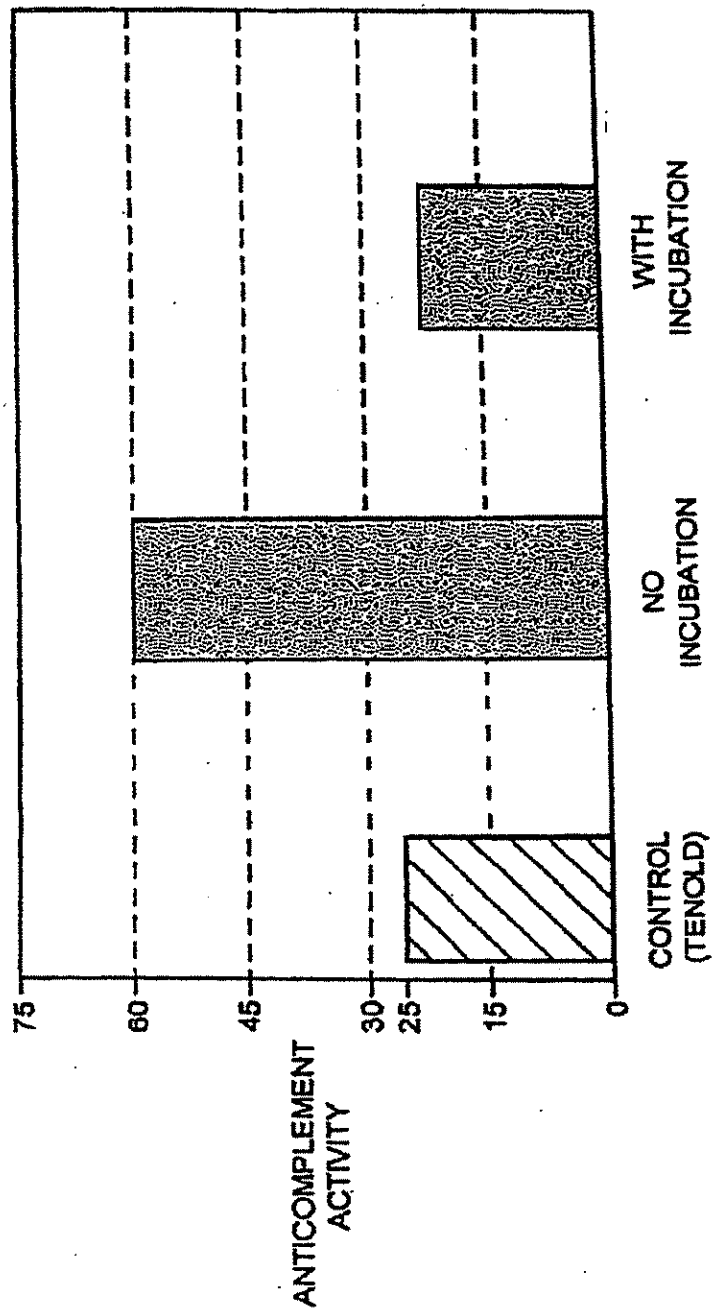
* cited by examiner

Primary Examiner—Yvonne Eyler
(74) *Attorney, Agent, or Firm*—Connolly Bove Lodge & Hutz LLP

(57) **ABSTRACT**

Method of reducing the anticomplement activity (ACA) resulting from viral inactivation treatment of a solution of antibodies, the method comprising contacting the solution with a trialkylphosphate, such as tri-n-butyl phosphate, and a detergent, such as sodium cholate, under conditions sufficient to reduce substantially the virus activity, and then incubating the solution under controlled conditions of time, pH, temperature, and ionic strength such that the anticomplement activity is reduced to an acceptable level. In a preferred embodiment, the ACA is reduced to less than 60 CH_{50} units/mL, the incubation is for at least about ten days at a pH from 3.5 to 5.0, the temperature is maintained within a range of 2 to 50° C., and the ionic strength of the solution is less than about 0.001 M.

24 Claims, 1 Drawing Sheet


WITH INCUBATION
NO INCUBATION
CONTROL (TENOLD)
75
60
45
30
25
15
0
ANTICOMPLEMENT ACTIVITY

PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

BACKGROUND OF THE INVENTION

1. Field

This invention generally deals with an intravenously injectable immunoglobulin product, and more specifically deals with an intravenously injectable immune serum globulin (IGIV) which has been subjected to a virus inactivation step and which has a low level of anticomplement activity.

2. Background

Early pharmaceutical preparations of immune serum globulins could not be administered intravenously due to an unacceptably high incidence of adverse reactions. These adverse reactions were associated with a decrease in serum complement levels, apparently caused by complement binding to the administered gamma globulin. (1) The ability of gamma globulin to bind complement, or its anticomplement activity (ACA), is greatly increased as a result of denaturation brought about during the fractionation procedure. Several approaches have been taken to address the problem of rendering ISG safe for intravenous administration. (See (2) and references therein). Tenold reported a method of preparing an immune serum globulin (ISG) with low ACA which could be administered by intravenous injection. (2, incorporated herein by reference). The Tenold '608 process requires formulating the ISG at low ionic strength (preferably less than about 0.001) and at low pH (3.5–5.0).

Other methods of preparing intravenously injectable immune serum globulin (IGIV) have been reported, including stabilizing with carbohydrates such as maltose (3). A process including incubation of ISG at pH 4.0 at 37° C. (4) results in a product with low ACA which may be administered by intravenous injection; however, upon storage the product regains its high ACA. IGIV has also been prepared by covalent modification of the ISG, for example by proteolysis (5) or by reduction of disulfide linkages followed by reaction with a blocking agent (1,6).

Antibody preparations, since they are isolated blood products, have an inherent hazard of transmitting virally-mediated diseases. Inactivation of viruses is an important step in producing safe and effective blood products. U.S. Pat. No. 4,540,573 to Neurath et al., which is incorporated herein by reference, describes a viral inactivation process using a trialkyl phosphate and detergent process (hereinafter, the solvent/detergent process, or SD process). (7) That solvent/detergent method has gained acceptance as being efficacious in the inactivation of lipid-enveloped viruses with limited adverse effects on biological activity or blood product profile. (8, 15; See also 12 for a discussion of various viral inactivation processes).

Current antibody preparations on the market generally have been regarded as safe with respect to viral contamination. (9) This is thought to be due to features of the fractionation processes used to isolate these blood products. However, it would be desirable to further ensure the safety of the antibody preparations by including a distinct viral inactivation step in the production process. Successful reduction of viral activity in an IGIV solution was reported using several different methods of viral inactivation for a variety of viruses. (16, 17) A process for preparation of immunoglobulins substantially free of retrovirus has been reported involving incubation of ISG under controlled conditions of time, temperature, and pH. The process entails

isolating ISG via a cold ethanol plasma fractionation process and then storage of the ISG at one of two storage conditions: (a) at pH≦4.25 at a temperature of 27° C. for at least three days, or (b) at pH≦6.8 at a temperature of 45° C. for at least six hours. (10).

We have found that using the SD process to treat ISG preparations, especially those subsequently formulated according to the Tenold '608 patent, results in a product with an acceptable viral inactivation but with unacceptably high levels of ACA. Elevated ACA levels were always detected at the sterile bulk stage (i.e., after compounding as 5% or 10% IGIV and filtration with 0.2 μm sterile filters) of all tri-n-butyl phosphate (TNBP)/detergent treated IGIV preparations regardless of process scale. Preparations of ISG with high ACA levels are not suitable for intravenous injection and instead must be administered via other routes, e.g. intramuscular (IM) injection. However, IGIV preparations are more desirable since they are immediately available in the bloodstream and are not subject to loss associated with IM injection. It is thus desirable to have an IGIV product which is both low in ACA and has been subjected to a viral inactivation step.

SUMMARY OF THE INVENTION

The invention is a method for producing an intravenously injectable immune serum globulin (IGIV) preparation with low anticomplement activity which has been chemically treated to render it substantially free of lipid-enveloped viruses. The method comprises a solvent/detergent viral inactivation step followed by an incubation step. We have discovered that the incubation step is necessary to achieve an acceptable level of ACA low enough to allow the ISG to be administered by intravenous injection. The incubation step should be conducted under controlled time, pH, temperature, and ionic strength. Preferably, the pH should be maintained between about 3.5 and about 5.0, the temperature should be within a range of about 2 to about 50° C., and the ionic strength should be less than about 0.001M. In a preferred embodiment the ACA of the ISG preparation decreases gradually over a period of at least about ten days when the ISG is maintained at a pH of about 4.25 at low ionic strength (less than about 0.001M) and the viral inactivation step (in a model system) results in a substantial reduction (i.e. at least 4 logs) in the titer of lipid enveloped viruses.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 shows a comparison of the typical average observed ACA levels of 5% IGIV solutions treated according to the SD process and with or without the follow-up incubation of the present invention.

SPECIFIC EMBODIMENTS

Materials and Methods

The starting material for the process of this invention is unmodified human immune serum globulin. In the specification and claims the term "immune serum globulin" is used to define the substance also referred to in the literature variously as gamma globulin, IgG and immunoglobulin G. It consists predominantly and preferably of at least about 85 percent of the 7S species of gamma globulin, which has a molecular weight of about 160,000. Any remainder is preferably 9S species, with a molecular weight of about 300,000. Both standard immune and hyperimmune serum globulins, e.g., tetanus, rabies and hepatitis immune serum globulins,

can be employed, the solvent/detergent treated product being immune and hyperimmune ISG, respectively. Thus, a suitable starting material for the process of this invention is Cohn's Fraction II or Fraction III filtrate. (See Refs. 13, 14.)

Fraction II, by ultracentrifugation studies, is predominantly (about 85 percent) the 7S (sedimentation constant of 7) species of gamma globulin with an average molecular weight of 160,000. The remaining protein is essentially 9S material with a M.W. of about 300,000. Wet Fraction II paste (approximately 30 percent solids) is commonly lyophilized to obtain dry ISG powder which is then dissolved and prepared for intramuscular injection as a 16.5 percent sterile solution. Either the wet Fraction II paste or the dry ISG powder is a suitable starting material for the process of this invention.

Gamma globulin obtained by any process which has essentially the same composition of protein components as found in the Cohn Fraction II or Fraction III filtrate can be used as starting material in the present process. Both standard immune serum globulin and hyperimmune serum globulin can be employed as starting materials. As is well known, the latter is produced from plasma or serum obtained from selected donors who have much higher titers for a specific antibody than is normally found in the average population. These donors have either been recently immunized with a particular vaccine or else they have recently recovered from an infection or disease. These high titer sera or plasmas are pooled and subjected to the usual Cohn fractionation procedures up to the point of isolating Fraction II.

Furthermore, because the amount of antibody required to achieve a desired immunological response is substantially less when administered intravenously, it will be apparent the intravenous dose will be substantially less than the intramuscular dose which will produce the same serum antibody titer. Thus, the dose of intramuscular ISG and hyperimmune serum globulin must be higher than that required to achieve the same serum antibody titer when globulin of the same antibody activity is administered intravenously.

The starting wet paste or lyophilized powder is dissolved in a volume of water or other physiologically-acceptable carrier to provide a protein solution of a concentration of about 0.5–20% preferably about 5 to 10 percent. If Fraction III filtrate is employed, the aqueous solution must be concentrated by conventional techniques to the desired protein concentration. Any protein concentration may be used in this method; however, the above range is preferred from a practical standpoint.

After the protein has been dissolved or concentrated, the solution is adjusted to a pH of about 3.5 to 5.0 preferably about 3.8 to 4.2, by addition of a physiologically-acceptable acid such as hydrochloric acid. In general, the pH is adjusted to a point whereat the monomeric material in the protein solution is maintained at a maximum. However, the pH must not be so low as to result in gelation. The temperature should not be harmful to the ISG material. Good results are obtained within the temperature range of about 0–20° C. It is not necessary to hold the so-adjusted material for any period of time prior to the next step; however, the material may be held, if desired, without detrimental effects.

The protein solution at the appropriate pH (preferably 3.8–4.2) may be diafiltered with at least 4 volume exchanges of water to reduce the alcohol concentration from approximately 17% (Filtrate III) to about 2% alcohol. The efficacy of solvent/detergent as a viral inactivation method is much better at or above ambient temperatures; however, high concentrations of alcohol at these temperatures will denature the IgG molecules. Thus, this inactivation must be performed in low alcohol concentration.

Next, the protein concentration of the so-treated material is adjusted to the level desired for incubation with TNBP/detergent, generally less than 10% protein for maximum viral inactivation. This adjustment is accomplished by conventional techniques not detrimental to ISG, e.g., ultrafiltration, reverse osmosis, sublimation, evaporation, etc. Prior to addition of TNBP/detergent, the pH may be adjusted within a wide range, depending on the detergent to be used. With Tween 80, the pH may be as low as 3.5, where the IgG starts becoming unstable. With cholate, the pH is adjusted to within the range of 5.0–6.4, preferably about 5.6, prior to addition of TNBP/detergent. Satisfactory cholate solubility during incubation was achieved by adjusting the immunoglobulin solutions to a pH of 5.5 or higher prior to addition of TNBP and sodium cholate. Adjusting the IgG solution to pH values lower than 5.5 is not suitable because the solubility of sodium cholate is highly dependent on pH (cholic acid pK=6.4), with poor solubility at pH 5.5 or lower. Furthermore, maximum viral inactivation during incubation with TNBP/cholate was observed at pH values less than 6.0 in experiments which employed model viruses spiked into IgG solutions. The inactivation of HIV-1 and BVDV (bovine viral diarrhea virus, which is employed as a model for hepatitis C) was accelerated at pH 5.8, with inactivation to the detection limit occurring in 1–2 hours, whereas inactivation to the detection limit required a minimum of 6 hours when pH 7 conditions were used.

Next, the TNBP/detergent is added to the protein solution (preferably less than 8% [w/w], pH 5.8) mixed thoroughly, and then incubated above ambient temperatures, for example 30° C., with continuous agitation or mixing. Target TNBP/cholate levels for optimal viral inactivation during the incubation step should be >3 mg/mL TNBP and >2 mg/mL cholate as defined by Edwards et al. (8) Moreover, for effective viral inactivation, it is important that the solution is essentially free of particulates in order to facilitate thorough mixing of solvent/detergent and IgG solution. After incubation with TNBP/cholate under these conditions, greater than 5.2 $\log_{10}$ reduction of HIV-1 and greater than 4.0 $\log_{10}$ reduction of BVDV were detected.

After completing the incubation which provides the viral inactivation, the solvent and detergent molecules must be removed in order to achieve a final product with low levels of residual TNBP and cholate which would be suitable for intravenous administration. Generally, procedures to remove detergent are also effective in removing TNBP, and vice versa. Very low levels of TNBP and cholate in the final container can be achieved by a combination of filtration, diafiltration and hydrophobic chromatography. After completing the incubation, the majority of cholate (and TNBP) can be removed from the protein solution by filtration, providing the solution had been previously adjusted to a lower pH value such as 4.0, because sodium cholate is sparingly soluble in aqueous solutions at such pH values. Moreover, all processing steps which follow the solvent/detergent incubation are performed at lower pH values (i.e., 4.0) because IgG molecules are more stable at pH values between 3.5–5.0, in low ionic strength solutions. (2) Thus, after incubation with TNBP/cholate, the protein solution is adjusted to approximately pH 4.0 and incubated at 0–8° C. in order to promote cholate precipitation. Next, filtration is employed to remove the precipitated cholate from the IgG solution.

The so-treated solution is diafiltered with at least four volume exchanges of water to reduce the ionic strength and

to remove additional TNBP and cholate. After or during the above treatment, the pH is measured and maintained within the range of about 3.5–5.0. The protein concentration of the so-treated material is adjusted to 10–30%, usually 13% (w/v) by employing conventional techniques not detrimental to ISG, e.g., ultrafiltration, reverse osmosis, sublimation, evaporation, etc. Again the pH of the preparation is maintained within the range of about 3.5–5.0, preferably about 3.8–4.2.

In the present invention, hydrophobic chromatography is employed to remove the TNBP and cholate not eliminated by the filtration and diafiltration steps, and thus provide a final product with low levels of residual TNBP and cholate which is suitable for intravenous administration. Hydrophobic chromatography is a method for TNBP removal from protein solutions that has fewer drawbacks and limitations than other available methods such as oil extraction, ion exchange or affinity chromatography. In part, this is because the protein of interest (IgG) remains in solution throughout the TNBP removal process. Polystyrene-based resins (typically PLRP-S from Polymer Laboratories, Amherst, Mass.) were used to remove the solvent/detergent from solution, as we have found the polystyrene-based resins to be superior to other resins, such as silica-based C-18 resins.

Next, the ISG preparation is adjusted to 5% or 10% protein, and treated to render it ionic, i.e., to render it compatible with physiological conditions, or render it physiologically acceptable upon injection. In a preferred embodiment, the tonicity is adjusted to about 230 to about 490 mosmol/kg solvent. More preferably, the tonicity range is from about 250 to about 350 mosmol/kg solvent, and most preferably the tonicity range is from about 260 to about 325 mosmol/kg solvent. The 5% formulation (5% IGIV) is made tonic by the addition of 10% maltose. The 10% formulation contains 0.2 M glycine in order to achieve an isotonic preparation without large quantities of sugar. The product with either formulation (Gamimune®N 5% or Gamimune®N 10%) experiences shifts in molecular distribution (antibody aggregation) when the ionic strength of the low pH solution is increased. Therefore, sodium chloride, which is often used to achieve tonicity, should not be used.

The so-treated solution is incubated at pH 4.25 under low ionic strength conditions (NLT 21 days at 20–27° C. preferred) in order to provide a lowering of ACA levels. The ionic strength is determined according to Perrin (18), and in a preferred embodiment the ionic strength should be less than about 0.001M. Elevated ACA levels were always detected at this stage of all TNBP/cholate treated IGIV preparations (regardless of process scale); however, ACA levels are gradually lowered by incubation at pH 4.25 under low ionic strength conditions (Tables 3, 5–7). While there is no strict rule for determining when the ACA level is low enough to be an acceptable level suitable for intravenous administration, IGIV preparations should have ACA levels as low as possible.

The Figure depicts the typical average reduction of ACA observed in 5% IGIV solutions following SD treatment. For a 5% ISG formulation the acceptable level suitable for intravenous administration preferably would be less than about 45 CH_{50} units/mL, and more preferably less than about 30 CH_{50} units/mL. For a 10% ISG formulation, the acceptable level suitable for intravenous administration preferably would be less than about 60 CH_{50} units/mL, and more preferably less than about 45 CH_{50} units/mL. As used herein, one unit of ACA activity (one CH_{50} unit) is defined as the amount of protein capable of activating 50% of the complement in an optimally titered complement and red blood cell/hemolysin system. The assay measures the amount of complement that is bound by the mixture of standardized amounts of complement and protein. See refs. 19–20 for a discussion of the assay. Briefly, red blood cells that have been sensitized by preincubation with red blood cell antibodies are added to the complement/protein mixture. In the presence of free complement (not already bound by the protein) these sensitized cells will lyse, releasing hemoglobin which can be quantitated as a measure of the degree of lysis. In parallel, sensitized red blood cells are also added to a buffer control-complement mixture, whose degree of lysis is defined as 100%. The difference between the actual amount of complement needed to give 100% lysis and the amount of complement remaining unbound in the presence of protein equals the amount of complement actually bound by the protein, or anticomplement activity.

Results

Anticomplement Activity of ISG Resulting From Viral Inactivation Process

To establish the effect of the SD viral inactivation process on solutions containing ISG which are formulated according to the Tenold '608 patent, the experiments depicted in Table 1 were performed. The starting material (SM) was Cohn process filtrate III which had been ultrafiltered to about 5% protein and then diafiltered with four volumes of water.

In the control experiment, incubation (−)/SD (−), the SM was not subjected to any incubation or solvent/detergent treatment. In the incubation (+)/SD (−) experiment, the pH of the SM was adjusted to 7.0, the solution was incubated at 30° C. for ten hours, and then the pH was reduced to 4.0. In the incubation (+)/SD, TNBP & Tween 80 (+) experiment, the pH of the SM was adjusted to 7.0, 3 mg/mL TNBP and 2 mg/mL Tween 80 were added to the solution, the solution was incubated at 30° C. for ten hours, and then the pH was reduced to 4.0. In the incubation (+)/SD, TNBP & cholate (+) experiment, the pH of the SM was adjusted to 7.0, 3 mg/mL TNBP and 2 mg/mL cholate were added to the solution, the solution was incubated at 30° C. for ten hours, and then the pH was reduced to 4.0. The solutions in each experiment were then diafiltered with four volumes CWFI (cold water for injection) and concentrated by ultrafiltration. After addition of dry maltose to 10% w/v, the 5% IGIV solution (pH 4.25) was filtered through a 0.2 μm filter.

TABLE 1

Anticomplement activity in 5% IGIV produced by variations of the Solvent/Detergent IGIV Process

	ACA (CH_{50}/mL)
Control (no solvent/detergent treatment, no 30° C. incubation)	25
Incubate at 30° C. for 10 hr (no solvent/detergent)	22
Incubate at 30° C. for 10 hr NLT 3 mg/mL TNBP NLT 2 mg/mL Tween 80	68
Incubate at 30° C. for 10 hr NLT 3 mg/mL TNBP NLT 2 mg/mL cholate	>100

*These samples were assayed for ACA after final compounding according to the Tenold '608 patent, but they were not incubated at pH 4.25 and 22° C. prior to analysis.

The results listed in Table 1 show that levels of ACA increased in IgG samples after incubation with TNBP/cholate or TNBP/Tween 80. ACA levels were not elevated in IgG samples that were incubated for 10 hr at 30° C. in the

absence of solvent/detergent. These results suggest that ACA levels of IGIV samples were not elevated by either processing manipulations or incubation for 10 hr at 30° C. in the absence of solvent/detergent.

TABLE 2

Anticomplement activity in 5% IGIV spiked with TNBP/Na cholate

	ACA (CH_{50}/mL)
5% IGIV, no TNBP/cholate	12
5% IGIV with 100 μg/mL TNBP, 100 μg/mL Na cholate	13

Furthermore, spiking experiments (with TNBP and Na cholate, Table 2) have demonstrated that the elevated anticomplement activity levels were not artifacts caused by carrying out the anticomplement assay in the presence of trace levels of TNBP/Na cholate. Thus, using the prior art SD process for viral inactivation of a solution containing ISG, subsequently formulated according to the Tenold '608 patent, yields a product which has high ACA and is unsuitable for intravenous administration. In a similar experiment, SD treated samples which were not incubated (Table 3, Initial Testing) had ACA levels greater than 100 units.

TABLE 3

Reduction in Anticomplement activity of samples previously treated with TNBP/cholate

Sample	ACA (CH_{50}/mL) Initial Testing (no incubation)	ACA (CH_{50}/mL) After incubation 6 wk. @ 5° C. 3 wk. @ 22° C.
RB21872-16	>100	33
RB21872-17	>100	34
RB21872-18	>100	36
RB21872-20	>100	27

However, when duplicate SD treated samples were incubated for extended periods of time (6 weeks at 5° C. and 3 weeks at 22° C.), the level of ACA was markedly reduced (Table 3, after incubation). This led to further investigation of this surprising observation.

Aggregate Content of ISG Exposed to TNBP/cholate

The samples of the previous experiment (Table 3, Initial Testing) were analyzed by size exclusion (gel permeation) HPLC immediately after compounding to determine the extent of aggregation of the IGIV at the initial time point. HPLC analysis shows nearly complete monomer content in the samples. (Table 4).

TABLE 4

HPLC analysis of non-incubated 5% IGIV samples (Table 3 Initial)

Sample	Aggregate (%)	Dimer (%)	Monomer (%)	Fragment (%)
RB21872-16, initial	0.140	0.00	99.86	0.00
RB21872-17, initial	0.146	0.00	99.85	0.00
RB21872-18, initial	0.124	0.00	99.88	0.00
RB21872-20, initial	0.172	0.00	99.83	0.00

Previously, high IgG aggregate levels were shown to correlate with high anticomplement activity. However, results from analysis of the samples show the level of ACA in the samples to be greater than 100 units. (Table 3, 'Initial Testing') The HPLC analysis shows that the high ACA following the TNBP/cholate treatment was not due to the presence of aggregated IgG molecules.

Varied Conditions of Time and Temperature

The SM was the same as in the previous experiment, and experimental conditions were similar with the following changes. The solutions were treated with TNBP/cholate at pH 7.0 and then were compounded to 5% IGIV, 10% maltose, pH 4.25, as above. The ACA was assayed immediately after final compounding, after a first incubation for nine days at 5° C., and after a second incubation for 21 days at either 22° C. or 5° C. The results are presented in Table 5.

TABLE 5

ACA of TNBP/cholate treated IGIV samples

Sample Point	ACA (CH_{50}/mL)
Intermediate Samples	
Initial sterile bulk	>100
Incubated 9 d. @ 5° C.	>100
Final Incubation	
21 d. @ 22° C.	49
21 d. @ 5° C.	71

In the initial sterile bulk sample, which was treated with TNBP/cholate at pH 7.0, the level of ACA was again greater than 100 units for the initial time point, confirming the observations noted in Table 3. Upon incubation at 5° C. for nine days, the ACA remained greater than 100 units. The final incubation step at either 5° C. or 22° C. shows that the reduction in ACA is dependent on temperature, with faster reduction in ACA observed at higher temperatures.

Effect of pH During Solvent/detergent Treatment on ACA

ACA levels were evaluated after incubation with TNBP/cholate at pH 5.8 because better viricidal activity was observed at pH values less than 6.0. Generally, the non-incubated sterile bulk samples of material incubated at pH 5.8 had lower ACA levels than the pH 7.0 samples, but the trend of lowering ACA upon incubation was repeated in the pH 5.8 samples. In fact, the ACA levels continue to decrease beyond the 21 day incubation in samples that initially had elevated ACA levels after incubation with TNBP/cholate at pH 5.8 (Table 6). As was previously noted for the samples incubated at pH 7.0, the lowering of ACA was not due to decreasing levels of aggregated IgG molecules because the material treated at pH 5.8 was essentially monomeric IgG prior to 22° C. incubation (HPLC analysis, sample A4, Table 8).

TABLE 6

Sample A4 - ACA upon extended incubation

Incubation at 22° C. (days)	CH_{50}/mL
0	122
10	73
19	55
25	56
28	45
30	40
34	39
41	33

TABLE 6-continued

Sample A4 - ACA upon extended incubation

Incubation at 22° C. (days)	CH_{50}/mL
48	30
55	29

Similar results were achieved with samples formulated to 10% IGIV, 0.2 M glycine in the sterile bulk stage. Upon incubation at low ionic strength at pH 4.25 for 10 and 21 days, the levels of ACA were seen to decline in both 5% IGIV samples and 10% IGIV samples. (Table 7) The decrease in ACA can thus be observed over a range of ISG concentrations and over a range of pH values for the solvent/detergent treatment. (Tables 3, 5, 7) HPLC analysis (Table 8) of the sterile bulk samples presented in Table 7 confirmed that the elevated ACA levels were not due to aggregation of ISG molecules.

TABLE 7

ACA of samples treated with TNBP/cholate at pH 5.8

Sample	Sterile bulk (day zero) (CH_{50}/mL)	10 days incubation at 20–27° C. (CH_{50}/mL)	21 days incubation at 20–27° C. (CH_{50}/mL)
A1 (5% IGIV)	43	ND	10
A2 (5% IGIV)	31	14	15
A3 (5% IGIV)	44	15	12
A4 (5% IGIV)	122	73	55
B1 (10% IGIV)	>100	48	46
B2 (10% IGIV)	49	36	30
B3 (10% IGIV)	53	ND	37

Taken together, the above results suggest that ISG products which have been subjected to a solvent/detergent viral inactivation process resulting in an undesirable ACA increase can be made suitable for IV administration by incorporating an additional incubation step under the conditions described here to reduce the ACA to an acceptable level.

TABLE 8

HPLC Analysis of sterile bulk samples treated with TNBP/cholate at pH 5.8

Sample	Aggregate (%)	Dimer (%)	Monomer (%)	Fragment (%)
A2	0.140	0.00	99.86	0.00
A3	0.146	0.00	99.85	0.00
A4	0.124	0.00	99.88	0.00

CONCLUSION

The ACA increase resulting from the solvent/detergent treatment of the IGIV (antibody) solution appears to be an unavoidable secondary effect of TNBP/detergent treatment to inactivate viruses in the solution. I have discovered that by incubating the solution of IGIV at low pH (4.25) and low ionic strength (0.001M) for a relatively long period of time (at least about 10 days), the ACA gradually decreases over the period of incubation.

The prior art discloses a method of producing IGIV (the Tenold '608 patent) using low pH and low ionic strength. The Tenold '608 method omits the viral inactivation step, and thus avoids the problem of increased ACA, but the possibility of viral activity remains. Unlike Tenold, incubation is an essential aspect of the present invention for reducing the ACA.

The Neurath et al. '573 patent teaches the solvent/detergent viral inactivation step. However, Neurath '573 does not mention controlling the pH and also does not mention any consequences of the process relating to ACA. Elevated ACA levels were detected at the sterile bulk stage of TNBP/cholate treated IGIV preparations. However, ACA levels decreased upon incubation for at least about 10 days at pH 4.25, low ionic strength, and not less than about 20° C. (See Tables 5–7) The prior art describes several approaches to lowering ACA levels of purified IgG preparations, including removal of IgG aggregates. (11) IgG aggregates have been shown to activate the complement system in vivo. (1) In the present invention, however, lowering of IgG ACA was not due to decreasing levels of IgG aggregates because these TNBP/cholate treated IGIV preparations contained low levels of aggregated IgG (as measured by HPLC, Tables 4, 8) prior to incubation under such conditions.

It would be desirable to produce substantially virus-free IGIV, but following the prior art results in a product with an unacceptable level of ACA. Note that Tenold '608 states that the product is substantially free of ACA, but use of the SD process in conjunction with Tenold '608 does result in high levels of ACA: experimental results reported here show that treating ISG solutions with the SD process and then formulation according to the Tenold '608 patent leads to a product with high ACA. (See Tables 1, 3, 5–7) The surprising finding reported here is that a follow-up (terminal) incubation step lowers the ACA of the solvent/detergent treated solution. The typical average observed ACA levels of 5% IGIV solutions treated according to the SD process and with or without the follow-up incubation are compared in the Figure. The present invention thus includes a previously unobserved method of reducing the ACA by incubating under controlled conditions of pH, temperature, and ionic strength for a period of time, thus allowing the product to be administered by intravenous injection.

Mitra '714 does not suggest the use of a S/D process but, instead, reports that a relatively brief incubation of an ISG product under similar conditions results in a substantially virus free preparation. (10) However, employing incubation under such conditions to provide a lowering of anticomplement activity is a novel application of these incubation conditions which were previously employed in the IGIV process for inactivation of enveloped viruses.

The newly developed IGIV process reported here, which includes an additional internationally accepted viral inactivation procedure (treatment with TNBP/cholate), generates IgG preparations which have low ACA levels and are suitable for IV administration. The major advantage is that an IGIV product with improved safety can be obtained by a two-step process that includes a TNBP/cholate treatment for viral inactivation and incubation under conditions that afford low ACA levels that are suitable for IV administration.

The above disclosure is intended to illustrate the invention, and it is thought variations will occur to those skilled in the art. Accordingly, it is intended that the scope of the invention should be limited only by the claims below.

REFERENCES

1 Barandun, S. et al., *Vox Sang.* 7: 157–174 (1962).
2 Tenold, R. A., U.S. Pat. No. 4,396,608 (Aug. 2, 1983).

3 Fernandes, P. M. et al., U.S. Pat. No. 4,186,192 (Jan. 29, 1980).
4 Malgras, J. et al., *Rev. Franc. Trans.* 13: 173 (1970).
5 Sgouris, J. T., *Vox Sang.* 13: 71 (1967).
6 Pappenhagen, A. R. et al., U.S. Pat. No. 3,903,262 (Sep. 2, 1975).
7 Neurath, A. R. and Horowitz, B., U.S. Pat. No. 4,540,573 (Sep. 10, 1985).
8 Edwards, C. A. et al., *Vox Sang.* 52: 53–59 (1987).
9 Louie, R. E. et al., *Biologicals* 22: 13–19 (1994).
10 Mitra, G. and Mozen, M., U.S. Pat. No. 4,762,714 (Aug. 9, 1988).
11 Polson, A. and Ruiz-Bravo, C., *Vox Sang.* 23: 107–118 (1972).
12 Seng, R. L. and Lundblad, J. L., U.S. Pat. No. 4,939,176 (Jul. 3, 1990)
13 Cohn et al., *J. Am. Chem. Soc.* 68: 459 (1946).
14 Oncley et al., *J. Am. Chem. Soc.* 71: 541 (1949).
15 Kameyama, S. et al., U.S. Pat. No. 5,151,499 (Sep. 29, 1992).
16 Uemura, Y. et al., *Vox Sang.* 67: 246–254 (1994).
17 Yang, Y. H. J. et al., *Vox Sang.* 67: 337–344 (1994).
18 Perrin, D. D. and Dempsy, B., Buffers for pH and Metal Ion Control (Chapman and Hall, London, 1974), pp. 6–7.
19 Palmer, D. F. and Whaley, S. D., *Complement Fixation Test*, in Manual of Clinical Laboratory Immunology (Ed. N. R. Rose, et al., American Society for Microbiology, Washington, D.C., 1986) pp. 57–66.
20 Mayer, M. M., *Quantitative C'Fixation Analysis, Complement and Complement Fixation*, in Experimental Immunochemistry (Ed. E. A. Kabat and M. M. Meyer, Thomas, Springfield, Ill., 1961). pp. 214–216, 227–228.

What is claimed is:

1. A method of treating a solution of antibodies which may have virus activity, the method comprising

a) contacting the solution with a trialkylphosphate and a detergent under conditions sufficient to substantially reduce any virus activity and resulting in an increased level of anticomplement activity; and

b) then incubating the solution of step a) under conditions of controlled time, pH, temperature, and ionic strength, such that the increased anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration.

2. The method of claim 1, wherein the anticomplement activity is reduced to less than about 60 CH_{50} units/mL.

3. The method of claim 1, wherein the solution comprises about 5% wt./wt. antibody and the anticomplement activity is less than about 45 CH_{50} units/mL.

4. The method of claim 3, wherein the solution comprises about 5% wt./wt. antibody and the anticomplement activity is less than about 30 CH_{50} units/mL.

5. The method of claim 1, wherein the solution comprises about 10% wt./wt. antibody and the anticomplement activity is less than about 60 CH_{50} units/mL.

6. The method of claim 5, wherein the solution comprises about 10% wt./wt. antibody and the anticomplement activity is less than about 45 CH_{50} units/mL.

7. The method of claim 1, wherein the incubation is for at least about ten days.

8. The method of claim 1, wherein the pH is maintained within a range of about 3.5 to about 5.0.

9. The method of claim 1, wherein the temperature is maintained within a range of 2° C. to 50° C.

10. The method of claim 1, wherein the ionic strength is less than about 0.001 M.

11. The method of claim 1, wherein at least about 99% of the antibodies are monomeric.

12. The method of claim 1, comprising the further step of adjusting the tonicity of the solution to a physiologic value under such conditions that the ionic strength is not appreciably altered.

13. The method of claim 12, wherein the tonicity of the solution is adjusted by adding a carbohydrate to the solution.

14. The method of claim 13, wherein the carbohydrate used is maltose.

15. The method of claim 12, wherein the tonicity of the solution is adjusted to a range of about 230 to about 490 mosmol/kg solvent.

16. The method of claim 15, wherein the tonicity of the solution is adjusted to a range of about 274 to about 309 mosmol/kg solvent.

17. The method of claim 12, wherein the tonicity of the solution is adjusted by adding an amino acid to the solution.

18. The method of claim 17, wherein the amino acid used is glycine.

19. The method of claim 1, wherein the trialkylphosphate is tri-n-butyl phosphate and the detergent is selected from polysorbate 80 and sodium cholate.

20. The method of claim 1, wherein the solution has a pH between about 3.5 and about 6.0 during step a).

21. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength less than about 0.001 M, a pH between about 3.5 and about 5.0, an antibody concentration of about 5% wt./wt., and a maltose concentration of about 10% wt./wt.

22. The preparation of claim 21, wherein the pH is about 4.25.

23. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength less than about 0.001, a pH between about 3.5 and about 5.0, an antibody concentration of about 10% wt./wt., and a glycine concentration of about 0.2 M.

24. The preparation of claim 23, wherein the pH is about 4.25.

* * * * *

EXHIBIT 2

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 9

Application Number: 08/532211

Filing Date: 9/22/95

Appellant(s): William R. Alonso

James A. Giblin

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 2/20/97.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

The rejection of claims 1, 3-6, 10, 21 and 23 under 35 U.S.C. 112 as vague and indefinite is withdrawn.

Claims 1-24 stand rejected under 35 U.S.C. 103 as unpatentable over Tenold (U.S. 4,396,608) in view of Neurath et al (U.S. 4,540,573), Mitra et al (U.S. 4,762,714) and Joy Yang et al. (Vox Sang. 67:337).

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because claims 21-24 are dependent claims defining a product made by the process of claim 1. The product, as claimed, could not be infringed without also infringing the claimed method. Further, should the method of making the product be obvious, so too would the inherently resulting product made by using the method be obvious as well.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal. The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4396608	Tenold	8/2/93
4540573	Neurath et al	9/10/85

4762714 Mitra et al 8/9/88

Joy Yang, Y.H. et al. "Antibody Fc functional activity of intravenous immunoglobulin preparations treated with solvent-detergent for virus inactivation" Vox Sang, Vol. 67, (May 17, 1994) pp. 337-334.

(10) New Prior Art

No new prior art has been applied in this examiner's answer.

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The rejection of Claims 1, 3-6, 10, 21 and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn.

Claims 1-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Tenold (U.S. # 4,396,608) in view of Neurath et al (U.S.# 4,540,573), Mitra et al (U.S.#4,762,714), and Joy Yang et al (Vox Sang 67:337-344, 1994).

Tenold et al teach the modification of immune serum globulin (a solution of antibodies purified from blood plasma) to reduce anticomplement activity so that the solution may be safely administered intravenously. The starting material for Tenold's modifications is human immune serum globulin purified by Cohn's method, either fraction II or III. The starting solution is diluted in a physiologically acceptable carrier so as to obtain a protein or antibody

concentration of about 0.5-20%. The pH of the solution is than adjusted, and maintained, at about 3.5 to 5.0 with a physiologically acceptable acid such as hydrochloric acid. The temperature range is maintained at about 0-20 degrees C. The ionic strength of the solution is adjusted to less than 0.001 and the tonicity is adjusted, without altering the ionic strength, by addition of an amino acid such as glycine or a carbohydrate such as maltose. The specific osmolality of the final isotonic solution is not specified but the acceptable range to maintain tonicity would be well known and conventional to one of ordinary skill in the art. The final product obtained by the method of Tenold is an immune serum globulin, maintained at a controlled pH, temperature, ionic strength and tonicity so as to generate a monomeric solution of antibodies with a reduced anticomplement activity rendering the solution safe for intravenous administration. While Tenold does not incubate the solution at the given pH and temperature prior to the adjustment of ionic strength and tonicity, the pH and temperature are maintained throughout the procedure and the antibody solution is stored for up to six months under the defined controlled parameters. (see column 4 line 24 to column 8, line 54) The measured anticomplement activity of the immune serum globulin produced by Tenold's method is 3 mg protein per CH50 unit, which is less than 30,45 and 60 units. Tenold differs from the instant invention in that the starting material is not pre-treated to inactivate any infectious agents which may be present.

Neurath et al teach a method for the inactivation of infectious virus present in blood or blood derived solutions while maintaining the activity of proteins contained in the composition.

The method comprises treating the solution with a trialkylphosphate, for example tri-n-butyl phosphate and a wetting agent such as a detergent for example polysorbate 80 or sodium deoxycholate followed by removal of the inactivating agents and optional further processing of the product. The starting material for the method of Neurath et al may include fraction II or III of the Cohn purification to obtain immune serum globulin which is virus free (see the abstract, column 1 lines 5-20, column 4 lines 50-60, column 6 lines 40-61, column 7 to 8 and column 9 lines 19-25)

Mitra et al discuss the need to produce virus-free immune serum globulin solutions to assure that active viruses are not transmitted to patients. They follow the inactivation of spiked fraction II and III samples as the immune serum globulin solution is purified. They further specify that in order to obtain an immune serum globulin which is safe and effective for IV administration, the anticomplement activity of the solution must be reduced. They further specify that this may be accomplished through careful pH and ionic strength control (see column 1).

Joy Yang et al disclose a third-generation immune serum globulin for IV administration which includes a deliberate virus inactivation step of treatment with a solvent/detergent, specifically tri-n-butyl phosphate/polysorbate 80) (see the abstract and p.338, column 1). Joy Yang et al further discuss the desirability of retaining full Fc functions in a immune serum globulin preparation, including complement activity. Various assays are presented which evaluate the retention of Fc functions following the solvent/detergent treatment. An hemolysis

test indicates that, in their system, the complement mediated lysis of erythrocytes is not affected by the solvent/detergent virus inactivation step, see p. 339, column 2). Joy Yang et al do not teach the further adjustment of the immune serum globulin product to reduce anticomplement activity, but do stress the importance of full complement activity to the effectiveness of an immune serum globulin solution.

It would have been *prmia facie* obvious to and one of ordinary skill in the art would have been motivated, at the time the invention was made, to modify the method and resultant immune serum globulin product of Tenold et al by pretreatment of the antibody solution with a solvent/detergent as taught by Neurath et al or Joy Yang et al to ensure inactivation of infectious virus which is taught to be desirable by Mitra et al and to maintain a low anticomplement activity which is taught to be desirable by Mitra et al and Joy Yang et al.

(12) New Ground of Rejection

This examiner's answer does not contain any new ground of rejection.

(13) Response to argument

REJECTIONS UNDER 35 U.S.C. 112:

Appellant's arguments with regard to the rejection of claims 1, 3-6, 10, 21 and 23 are rendered moot by the withdrawal of the grounds of rejection.

REJECTIONS UNDER 35 U.S.C. 103:

Appellant's argue that there is no suggestion or motivation in the art to combine the teachings of Neurath et al. with the teachings of Tenold because the instantly observed increase

in ACA levels was unexpected and not taught in the prior art. Appellant's further argue, that even if the increase in ACA levels were expected, there was no suggestion in the art teaching the solution to the problem.

Appellant's arguments have been considered but are not found to be persuasive. While none of the prior art teaches an increase in ACA activity after viral inactivation by treatment with trialkylphosphate and detergent, the prior art in all cases indicates that it was art-standard knowledge that the level of ACA activity must be low for the serum globulin to be injected I.V. Tenold teach the undesirability of high levels of ACA activity and the necessity to assay for ACA activity and lower ACA activity before administration. (See column 1, lines 15-22 and column 2, lines 21-32). The method disclosed by Tenold et al to lower ACA activity is of record and is set forth supra. Mitra et al teach the desirability to prepare virus-free immune globulin compositions and further teach that ACA activity in such compositions was undesirable and must be eliminated, thus suggesting the combination of anti-viral treatment and the reduction of ACA levels. (See especially column 1, lines 23-45). Joy Yang et al in addition to teaching the desirability of viral inactivation of immune globulin compositions teach "it is clear the retention of the full range of Fc function is a prime requirement for therapeutic applications of IGIV.", i.e. ACA activity must be low. (See page 337, column 2, lines 1-3). Thus, the need to virally inactivate immune globulin compositions and to obtain immune compositions with low levels of ACA activity was known at the time the invention was made. Irregardless of the cause of the increased ACA level, it was art standard to measure

and lower levels of ACA in immune globulin preparations. The desirability of virus-free immune globulin compositions (blood products) was recognized. Neurath et al teaches a method of virally inactivating blood products. It would have been *prima facie* obvious and one of ordinary skill would have been motivated to treat immune globulin (solutions of antibodies) to inactivate viruses as taught by Neurath et al. Further, irregardless of whether it was expected that the anti-viral treatment of Neurath et al would result in increased ACA levels, the undesirability of high ACA levels was known and the need to measure ACA levels and lower them was known, thus providing motivation to combine the teachings of Tenold and Neurath, as taught by Tenold, Mitra et al, and Joy Yang et al. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Dillon*, 16 USPQ2d 1897 (Fed. Cir. 1990) and MPEP 2144.

Therefore, it is maintained that It would have been *prmia facie* obvious to and one of ordinary skill in the art would have been motivated, at the time the invention was made, to modify the method and resultant immune serum globulin product of Tenold et al by pretreatment of the antibody solution with a solvent/detergent as taught by Neurath et al or Joy Yang et al to ensure inactivation of infectious virus which is taught to be desirable by Mitra et al and to maintain a low anticomplement activity which is taught to be desirable by Mitra et al and Joy Yang et al.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Yvonne Eyler, Ph.D.
Patent Examiner
Group 1800

December 23, 1997

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EXHIBIT 3

Office Action Summary	Application No. 08/532,211	Applicant(s) Alonso
	Examiner Yvonne Eyler	Group Art Unit 1806

☒ Responsive to communication(s) filed on *May 14, 1996*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

PAGE 82

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Claims 1-24 are pending in the application.

Claim Rejections - 35 USC § 112

1. The rejection of claims 1, 3-6, 10, 21, and 23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the inventionis maintained.

Claim 1 was rejected as vague and indefinite in the recitations "a given level of anticomplement activity" and "an acceptable level suitable for intravenous administration."

The claim language was amended to recite "a given increased level of anticomplement activity." Further, it was argued that "an acceptable level" is not vague because it depends on the concentration of IGIV.

The latter argument is found to be persuasive, and the rejection based on "an acceptable level suitable for intravenous administration" is withdrawn based on the definition of an acceptable level found in the specification at page 9.

The amended recitation "a given increased level of anticomplement activity" is still found to be vague and indefinite. The use of the term given indicates that the level of anticomplement activity refered to is a precise value which is not included in the claim language, and therefore, it cannot be determined to what the term "given" is referring. Secondly, the incorporation of the term "increased", while more closely

reflecting the invention, does not include a standard against which an increase may be measured.

Claim 10 was found to be vague and indefinite because it recites an "ionic strength less than about 0.001" but fails to define what type of measure or what type of units are associated with the figure 0.001.

Claims 3-6, 21 and 23 refer to a solution comprises either 5% wt/wt antibody or 10% wt/wt antibody. This limitation is vague and indefinite because it is unclear to what the wt/wt refers. If the antibody is in an aqueous solution, then in would be wt/vol. If it is measured as wt/wt, it is unclear what the antibody is being measured with respect to.

Claim Rejections - 35 USC § 103

2. The rejection of claims 1-24 under 35 U.S.C. § 103 as being unpatentable over Tenold (U.S. # 4,396,608) in view of Neurath et al (U.S.# 4,540,573), Mitra et al (U.S.#4,762,714), and Joy Yang et al (Vox Sang 67:337-344, 1994) is maintained.

The claims are drawn to a method of preparing an immune serum globulin solution by first virally inactivating and then incubating under controlled conditions of pH, temperature and tonicity to obtain a low enough level of anticomplement activity to be injected IV.

Applicants argue that the prior art does not teach that the anticomplement activity of the serum preparation actually increases after viral inactivation and must be lowered again by controlled pH, temperature, and tonicity.

While none of the cited art specifically teaches an increase in anticomplement activity after viral inactivation, Neurath et al, Mitra et al, and Joy Yang et al teach the desirabilty of viral inactivation and Neurath et al and Joy Yang et al teach inactivation by solvent/detergent treatment. The prior art in all cases indicates that the level of anticomplement activity must be low for the serum globulin to be injected IV. Tenold et al and Mitra et al teach the reduction of anticomplement activity by incubation under controlled pH, temperature, and tonicity for an extended period of time. Mitra et al teaches to do so after viral inactivation. Thus while the references do not require that the anticomplement activity increase as a result of viral inactivation, such increase subsequently needing to be reduced, it would be obvious to one of skill in the art to monitor anticomplement activity (after viral inactivation or other manipulations) and to treat under conditions of controlled pH, temperature, and tonicity as taught by Tenold et al and Mitra et al to reduce the activity.

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Toni R. Scheiner

Yvonne Eyler, Ph.D.
August 15, 1996

TONI R. SCHEINER
PRIMARY EXAMINER
GROUP 1800

EXHIBIT 4

PATENT
MSB-7232

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

APPEAL BRIEF

EXAMINER: Y. EYLER

ART UNIT: 1806

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a Brief (3 copies) supporting an appeal from the final rejection mailed July 17, 1996. Authorization is hereby given to charge deposit account 03-4000 the $300.00 Brief Filing Fee under 37 CFR 1.17(f).

(1) REAL PARTY IN INTEREST: The real party in interest is the designated assignee of the application, Bayer Corporation.

(2) RELATED APPEALS AND INTERFERENCES: There are no related Appeals or Interferences regarding the Application.

(3) STATUS OF CLAIMS: Claims 1 through 24, the only claims pending, stand under final rejection. These claims are shown in the attached Appendix.

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PATENT
MSB-7232

Luajuana Riley, do hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail on the date indicated below and is addressed to the Commissioner of Patents and Trademarks, Washington, D. C. 20231.

Luajuana Riley

Luajuana Riley

February 17, 1997

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

APPEAL BRIEF

EXAMINER: Y. EYLER

ART UNIT: 1806

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a Brief (3 copies) supporting an appeal from the final rejection mailed July 17, 1996. Authorization is hereby given to charge deposit account 03-4000 the $300.00 Brief Filing Fee under 37 CFR 1.17(f).

(1) REAL PARTY IN INTEREST: The real party in interest is the designated assignee of the application, Bayer Corporation.

(2) RELATED APPEALS AND INTERFERENCES: There are no related Appeals or Interferences regarding the Application.

(3) STATUS OF CLAIMS: Claims 1 through 24, the only claims pending, stand under final rejection. These claims are shown in the attached Appendix.

(4) STATUS OF AMENDMENTS: An Amendment after Final Rejection was requested. The Examiner advised that the requested amendments would be entered upon the filing of a Notice of Appeal and this Appeal Brief. That amendment is reflected in the claims of the Appendix.

(5) SUMMARY OF INVENTION: The invention is a method of reducing undesirable anticomplement activity (ACA) resulting from the use of a trialkylphosphate for viral inactivation of a solution of antibodies. The method comprises contacting the solution with the trialkylphosphate under conditions assuring viral inactivation and resulting in an increase in ACA and then incubating the solution under controlled conditions of time, pH, temperature, and ionic strength such that the anticomplement activity is reduced to an acceptable level for intravenous administration of the solution of antibodies. An acceptable ACA level for intravenous administration depends on the antibody concentration. See page 9, lines 14-23 and claims 2-6. The steps of the invention are described in more detail in the Abstract, the Summary of Invention on page 3, lines 8-20 and the claims.

(6) ISSUES: Whether claims 1, 3-6, 10, 21 and 23 should stand rejected under 35 U.S.C. § 112 as vague and indefinite.

Whether claims 1 through 24 should stand rejected under 35 U.S.C. § 103 as unpatentable over Tenold (U.S. 4,396,608) in view of Neurath et al. (U.S. 4,540,573), Mitra et al. (U.S. 4,762,714) and Joy Yang et al. (Vox Sang. 67:337).

(7) GROUPING OF CLAIMS: Claims 1-20 are directed to the method of the invention and stand separate from product by process claims 21-24.

(8) ARGUMENTS:

REJECTIONS UNDER 35 U.S.C. § 112 (second paragraph): Claims 1, 3-6, 10, 21 and 23 were rejected as vague and indefinite in use of the expression, "a given increased level of anticomplement activity". Since the word "given" no longer appears in the claims due to entry of the requested amendment after final, the only issue remaining is whether use of the word "increased" is vague and indefinite on the ground there is no standard against which an increase may be measured. It is respectfully submitted that the "standard" in this application would be the starting ACA level. Since step (a) of the claimed methods results in an increase in ACA from the starting material, a standard is provided. If there is no such increase, then step (b) of the invention, and the invention itself, is not even needed. To illustrate this "standard", the applicant provided in his response of May 9, 1996, a marked up copy of the figure and referred to Table 1 on page 11 to show the "standard" used in that example. A copy of that marked up figure is enclosed with this Brief.

The examiner also objected to the designation of "wt./wt." in claims 3-6, 21, and 23 on the ground it was unclear what the wt./wt. referred to. It is clear from the application and examples that the invention is concerned with treating an aqueous solution of antibodies. Thus, the wt./wt. designation refers to the weight of antibodies (or protein) in a given weight of solution, expressed in a percent basis as is conventional in the art. Basis for an --aqueous-- solution can be found in the second full paragraph on page 5. See also page 7, seventh line from the bottom. Thus, the reference to either a 5% or 10% wt./wt. designation of the antibody solutions of claims 3-6, 21 and 23 clearly refers to the weight of antibodies per weight of solution. See also, Fritz and Schenk, Quantitative Chemistry, p. 8 (copy enclosed) for the definition of weight per cent concentration as it is known in the art.

In view of the amendments and the above arguments, the rejection of claims 1, 3-6, 10, 21 and 23 as being vague and indefinite under 35 USC 112 is improper.

REJECTIONS UNDER 35 USC 103: Although it may have been an obvious step to combine the TNBP viral inactivation teachings of Neurath et al. with the immune globulin of Tenold, this would only result in step (a). There is no suggestion or motivation to take the process one step further by requiring an incubation step (b). The increase in ACA caused by using TNBP in step (a) was unexpected. A combination of the art as suggested by the examiner assumes the ACA increase was expected. There is no evidence to support that assumption.

Even if the ACA increase could have been expected, it would not have suggested the claims. The claimed invention requires that the conditions pH, temperature and ionic strength of step (b) be selected to reduce the ACA to an acceptable level for IV administration. As pointed out on page 9, an acceptable level of ACA will depend on the weight of protein in the solution that is being treated. There is no evidence the prior art even recognized the problem, much less the solution to the problem as described in the claims. Thus, the combination of selected portions of Tenold and Mitra with the viral inactivation of Neurath et al. and Joy Yang et al. requires the use of hindsight. This is clearly impermissible to support a rejection under 35 USC 103.

In the enclosed revised Figure (submitted earlier only to help understand the invention and not for purposes of being a Formal Drawing), the increased ACA observed when using the viral inactivation technique of Neurath et al. (see middle bar) was surprising. It was only by the applicant's discovery of the unexpected increase of ACA caused by step (a) that the follow up of step (b) was possible. In other words, if the immune globulin of Tenold were simply combined with the viral inactivation of Neurath et al., one skilled in the art would not have even expected the rise in ACA, much less discovered a way to reduce it.

The examiner states that Tenold and Mitra et al. teach the reduction of ACA by incubation under controlled pHs, temperature, and tonicity for an extended period of time. Tenold teaches a formulation of IgG which yields a preparation already having low ACA which is stable for at least six months. Tenold does not teach how to obtain a decrease in ACA. Moreover, Tenold describes IgG aggregation as causing ACA. In the present invention, lowering of ACA was not due to decreased IgG aggregates because the TNBP/cholate treated IGIV preparations already contained low levels of aggregated IgG (as measured by HPLC) prior to incubation step of the invention.

Mitra et al. describe the antiviral action of incubation for at least 3 days at pH 4.25, low ionic strength, and 27°C. However, these authors do not disclose a lowering of IgG ACA due to such incubation conditions. Mitra et al. would not have recognized that TNBP treatment caused an increase in ACA and, by teaching a viral inactivation without chemical agents such as TNBP actually teach away from the claims.

In view of the above remarks, appellants respectfully urge that the rejection of claims 1 through 24 as being obvious under 35 U.S.C. § 103 was improper.

Respectfully submitted,

Dated: February 17, 1997

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EXHIBIT 5

Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM R. ALONSO

Appeal No. 2001-1485
Application No. 08/532,211

HEARD: MAY 22, 2003[1]

Before WILLIAM F. SMITH, ADAMS and MOORE, *Administrative Patent Judges.*

MOORE, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1 - 24, which are all of the claims pending in this application.

1 A request for oral hearing was made within the notice of appeal dated December 18, 1996. Although the appellant appears to have been charged the appeal and oral hearing fees on January 16, 1997, the request for oral hearing was not acted upon by the USPTO. As a historical note, we observe that at the time the request was filed, 37 CFR 1.194 (b) (1993) read "If appellant desires an oral hearing, appellant must file a written request . . ." 37 CFR 1.194 (b) (1997) now reads "If appellant desires an oral hearing, appellant must file, in a separate paper, a written request for such hearing . . ." Such oversights are now more easily avoided. We sincerely apologize for the delay in discovering the oral hearing request.

REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and reads as follows:

> 1. A method of treating a solution of antibodies which may have virus activity, the method comprising:
>
> a) contacting the solution with a trialkylphosphate and a detergent under conditions sufficient to substantially reduce any virus activity and resulting in an increased level of anticomplement activity; and
>
> b) then incubating the solution of step a) under conditions of controlled time, pH, temperature, and ionic strength, such that the increased anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration.

The References

In rejecting the claims under 35 U.S.C. § 103(a) the examiner relies upon the following references:

Tenold (Tenold)	4,396,608	Aug. 02, 1983
Neurath et al. (Neurath)	4,540,573	Sep. 10, 1985
Mitra et al. (Mitra)	4,762,714	Aug. 09, 1988

Joy Yang, Y.H. et al., "Antibody Fc Functioning Activity of Intravenous Immunoglobulin Preparations Treated with Solvent-Detergent for Virus Inactivation," Vox Sang, 1994; 67:337-344 (Joy Yang).

The Rejections

Claims 1-24 stand rejected under 35 U.S.C.§ 103(a) as being unpatentable over Tenold in view of Neurath, Mitra, and Joy Yang.

The Invention

The invention is directed to a method for treating a solution of antibodies which may have viral activity by a two-step process of first contacting the solution with a trialkylphosphate and detergent under conditions which reduce viral activity and increase anticomplement activity, then incubating the solution under controlled time, pH, temperature, and ionic strength to reduce the increased anticomplement activity. (Claim 1).

Discussion

The § 103 Rejection of Claims 1-24 over Tenold in view of Neurath, Mitra, and Joy Yang

The examiner has found that Tenold teaches the modification of immune serum globulin (ISG) to reduce anticomplement activity (ACA) in order that the serum may be administered safely. (Examiner's Answer, page 4, lines 15-17). The resulting ISG product is then maintained at a controlled pH, temperature, ionic strength, and tonicity so as to generate a monomeric solution of antibodies with a reduced ACA rendering the solution safe for intravenous administration (Id., page 5, lines 7-11).

The examiner has also found that Neurath discloses a method for inactivating infectious virus present in blood or blood derived solutions (including ISG) while maintaining the activity of proteins contained in the composition. This is accomplished by treating the solution with a trialkylphosphate and a detergent

followed by removal of the inactivating agents and further optional processing of the product. (Id., page 5, line 19 - page 6, line 7).

The examiner has additionally found that Mitra teaches the need to produce virus-free ISG to prevent viral infection in patients. Mitra also recognizes the historic need to reduce the ACA to obtain safe ISG. (Id., page 6, lines 8-14).

The examiner has further found that Joy Yang discloses an ISG with a deliberate virus inactivation step followed by retention of complement activity: (Id., page 6, line 15 - page 7, line 8).

The examiner thus concludes that it would have been obvious to one of ordinary skill at the time the invention was made to modify Tenold to pretreat for viral reduction as taught by Neurath, Mitra, and Joy Yang to both ensure reduction of viruses and low ACA. (Id., page 7, lines 6-11). As to the incubation step of Claim 1(b), the examiner explains that the ``antibody solution [of Tenold] is stored for up to six months under the defined controlled parameters,'' citing Tenold, column 4, line 24 - column 8, line 54).

The appellant, on the other hand, asserts that there is no suggestion or motivation to require a step (b) which reduces the increased ACA level as no one was aware of the ``surprising'' increase. Consequently, no one could have expected the increased ACA level, much less found a way to counter it. (Appeal Brief, page 4, lines 4-34).

The appellant also asserts that the Tenold and Mitra references do not teach a decrease in ACA, and Tenold blames the increase of ACA on aggregation of the monomers. (Id., page 5, lines 1-11). Mitra, it is urged, fails to disclose a lowering of ACA due to incubation conditions. (Id, page 5, lines 12-18).

We observe that it is not in dispute that the appellant's process combines two relatively well-known steps to accomplish known functions. Neurath is known to provide acceptable viral inactivation (Neurath, column 4, lines 1-18), and Tenold to provide ISG solutions with low ACA (Tenold, column 8, lines 8-10). Indeed, that is the basis for the examiner's rejection - inactivation of viruses and a low ACA are required for intravenous preparations - therefore it would have been obvious to pretreat the Tenold starting material to eliminate viruses. (Examiner's Answer, page 9, lines 1-20).

The examiner notes that none of the applied prior art teaches an increase in ACA activity after viral inactivation by treatment with trialkylphosphate and detergent, but also asserts that it was art-standard knowledge that the level of ACA must be low for the serum globulin to be injected intravenously (Examiner's Answer, page 8, lines 4-8).

However, the claimed subject matter requires that the inactivation step result in an increase in ACA levels, and a reduction in that claimed increase by the incubation step to a point where the solution is suitable for intravenous use. The

appellant argues that there is no motivation to require an incubation step (b) as the increase in ACA caused by using the solvent-detergent method was unexpected. (Appeal Brief, page 4, lines 8-10). The examiner has admitted that the prior art is silent on this claimed increase in ACA.

It is clear to us that the problems of viral presence in antibody solutions and the problems of reducing ACA to an acceptable level were well known, as discussed in the cited references. The solvent-detergent method of Neurath inactivates viruses, and the Tenold ACA reduction process reduces ACA. The appellant has admitted that the combination of the Neurath and Tenold procedures ``may have been an obvious step'' (Appeal Brief, page 4, lines 4-5) but that such combination ``would only result in step (a)'' (Id., page 4, lines 6-7).

The appellant has discovered that Neurath's process results in elevated ACA levels (Specification, page 17, last 2 lines). Although the ACA increase was unrecognized, Neurath alone therefore inherently meets step (a) of the process. Neurath also suggests ``further processing'' (column 9, lines 19-24). The question then presented is whether one of ordinary skill in the art would be taught to follow with the Tenold process and whether the instantly claimed results would be obtained.

Tenold discloses a method for reducing ACA in ISG to the point that the ISG is suitable for IV administration. This is accomplished by solubilizing an ISG to yield a solution with a

certain protein concentration. The pH and ionic strength of the solution is adjusted to the point where the monomer content of the ISG is greater than about 90% and the actual and latent ACA is such that the ISG product is IV injectable. (Tenold, column 4, lines 30-41). The examiner states that Tenold differs from the instant claims in that the starting material is not pre-treated to inactivate infectious agents (Examiner's Answer, page 5, lines 16-18). The appellant urges that Tenold already has a low ACA and consequently cannot reduce ACA. (Appeal Brief, page 5, lines 3-6).

Tenold also discloses storing the solutions at an ionic strength of 0.001, a pH of 4.2, at room temperature, and for a six-month period of time. (Tenold, column 9, lines 12-21). The specification reveals that the incubation is conducted at an ionic strength of 0.001, a pH of 4.25, at 20-27°C (room temperature), at not less than 21 days (Specification, page 9, lines 4-12). Thus, Tenold would appear to disclose the values required by step (b) to obtain the desired ACA goal.

Viewed alone, the relied upon teachings of the applied prior art may perhaps be said to support a conclusion of prima facie obviousness.

However, the specification establishes the following:

(1) Solvent detergent viral inactivation results in an increase in ACA (See Table 1, Specification, Page 11).

(2) Using the solvent detergent process to treat ISG and subsequently treating that product according to Tenold does not

result in a product having acceptable ACA levels when measured immediately. (Specification, paragraph bridging pages 2 and 3 and Table 5).

(3) In contrast, holding (``incubating'') the solvent-detergent inactivated samples results in marked lowering of ACA (Specification, page 12, Table 3).

(4) The ACA results do not appear to correlate to the monomer content (Specification, page 17, table 8).

(5) Tenold's basic process (starting with non-solvent detergent inactivated solutions) results in a 25 ACA (CH_{50}/mL). (Specification, page 11, table 1).

From this, it is apparent that the problem being addressed places the question of whether a prima facie case of obviousness exists in a different light. First, one must question whether the teachings and results of Tenold can be combined with Neurath successfully. See, for example, the paragraph bridging pages 2 and 3 of the specification. Tenold starts with an unmodified human ISG (Tenold, column 4, lines 65-66) initially having an ACA which is unacceptable for intravenous injection (although the actual ACA level is not specifically described) (Tenold, Column 1, lines 23-27). The ACA level is lowered such that the final product has an ACA which is acceptable immediately, without appreciable change in the monomer content after 6 months (Column 8, lines 8-10). From the evidence provided by the appellants, this ACA can initially be 25 (Specification, page 11, Table 1).

If one of skill in the art starts with the Neurath solvent detergent modified ISG, and further treats that product by the Tenold process, the ISG would apparently still have an unacceptable ACA level. (See specification, table 3, page 12).

The examiner does not dispute the data in the specification showing that simply treating a solvent detergent virally inactivated ISG solution obtained by way of the Neurath process will not have an acceptable ACA level immediately or shortly after being further treated by the procedure described in Tenold. Rather, the examiner relies upon the data reported after containers of the Tenold treated ISG had been stored for six months.

Specifically, Tenold states at column 9, lines 15-30 that initial results indicated that a monomer level of 99% had been achieved. That level of monomer content had been maintained for six months. How does the Tenold data compare with the data in the present specification? Not well.

The appellants state that they treated solvent detergent virally inactivated ISG obtained by way of the Neurath process with the Tenold ACA lowering procedure and that the resulting product did not have an initially acceptable ACA level. This is in direct contrast to Tenold's statements that the process initially provides an acceptable ACA. Confronted with this anomaly, why would one of ordinary skill in the art then further incubate the solvent detergent treated ISG having an unacceptable

ACA after the Tenold process?[2] On this record we find no reason to do so.

The six-month data in Tenold only shows that an initial acceptable ACA level can be maintained upon six months storage. Importantly, Tenold does not teach that the initially high ACA level may be lowered merely by storing the ISG for six months. Assuming the examiner is correct, and that one of skill in the art would measure ACA after Neurath's solvent detergent treatment, that person would presumably discover what the appellants did; the ISG has a higher ACA level than expected. Why, then would one skilled in the art know that simply treating the solvent detergent ISG by way of Tenold would not lower the ACA to an acceptable level, but rather a significant incubation step would be needed? Again Tenold only indicates that six months storage maintains, not lowers, the ACA level.

> ``Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious.'' In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

---

2 Although not discussed in the Examiner's Answer or the Brief, we observe that Mitra teaches a Cohn fractionated ISG, when stored, shows a reduction in the AIDS virus. (Column 6, lines 42-54 and column 7, line 1 to column 8, line 25). However, this storage does not occur after a solvent detergent inactivation step, and does not reveal the effect on the ACA of the ISG solution.

We think this is the case here. Once appellants did what the prior art would reasonably appear to suggest doing, they found they did not obtain the expected results. It was only after obtaining the anomalous results did they understand the problem and discover its solution.

The decision of the examiner is reversed.

Summary of Decision

The rejection of claims 1-24 under 35 U.S.C. §103(a) as being unpatentable over Tenold in view of Neurath, Mitra, and Joy Yang is reversed.

REVERSED

WILLIAM F. SMITH
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

JAMES T. MOORE
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

Appeal No. 2001-1485
Application No. 08/532,211

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EXHIBIT 6

1806

PATENT
MSB-7232

#3|A
10-2-96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

RESPONSE

PRIMARY EXAMINER: T. R. Scheiner

ART UNIT: 1800

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a response to the Official Action mailed February 9, 1996. Please enter the following amendment and remarks.

IN THE CLAIMS:

In claim 1, step (a), line 3, insert --increased-- before "level".

REMARKS

Basis for adding the word --increased-- to step (a) in sole independent claim 1 can be found on page 11 in the first line after Table 1.

RE THE REJECTIONS UNDER 35 USC 112: The expression "given level" of anticomplementary activity (ACA) has been modified to require that it be a "given increased level". It is submitted that the earlier bases for rejection under 112 on the grounds that the language is vague should be reconsidered and found inapplicable. The increased level is demonstrated in the Examples and Figure.

The expression "acceptable level" of ACA appearing in claim 1 satisfies the requirements of 35 USC 112 and is not vague language. The acceptable level of ACA generally depends on IGIV concentration and examples (for 5 and 10% IGIV solutions) are described in the second full paragraph of page 9.

RE THE REJECTION UNDER 35 USC 103: As may be appreciated by the Examiner, the origin of the invention is the discovery by the applicant that using the trialkyphosphate/detergent viral inactivation method of Neurath et al. for an immune globulin preparation resulted in a surprising but undesirable increase in ACA. To treat the immune globulin preparation in a manner that assures substantial reduction of viral activity (as defined in the application) the conditions of the treatment of step (a) results in an increased ACA level. This increase is now a requirement in step (a) of the claimed methods.

In step (b), the inventor requires that the product of step (a) be incubated under conditions sufficient to bring about a decrease in ACA to an acceptable level.

The Examiner appears to take the position that a combination of the solvent/detergent treatment of Neurath et al. when combined with the immune globulin preparation of Tenold would suggest the method claims under 35 USC 103. Applicants disagree.

The invention can be illustrated better perhaps by viewing the enclosed modified copy of the figure filed with this application. The only modification to the figure is the insertion of the value of ACA level in the control sample prior (corresponding to Tenold). See Table 1, page 11. This is shown to the left of the TNBP treatment represented by the center bar. Thus, in looking at the enclosed revised figure one can see that the original level of ACA in the control must be first increased by the TNBP treatment of step (a) followed by a decrease caused by the incubation requirements of step (b).

There is no suggestion in the prior art, alone or combined, that shows or suggests an increase in ACA level followed a decrease in ACA level to result in a viral inactivated immune globulin preparation with an acceptable ACA level. Thus, the main basis for rejection under 35 USC 102 (Tenold in view of Neurath et al.) should be reconsidered as no longer applicable.

OTHER REFERENCES: Since the Mitra et al. reference does not show the use of solvent/detergent for viral inactivation and since the Yang et al. article does not show or suggest conditions requiring an increase in ACA level followed by a decrease in ACA level it is submitted that those references would not add to any ground for rejecting the current claims, especially as amended.

In view of the above amendment and remarks, it is submitted that the claims in this application now define patentable subject matter and should be allowed.

PATENT
MSB-7232

If the Examiner responsible for this application has any questions regarding the above amendment or remarks that Examiner is invited to telephone the undersigned at anytime.

Respectfully submitted,

Dated: May 9, 1996

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EXHIBIT 7

PATENT
MSB-7232

5/B MJS 12/16/96 (AE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

REQUEST FOR AMENDMENT AFTER FINAL

EXAMINER: Y. EYLER

ART UNIT: 1806

OK TO ENTER 12/17/96 12/19/96

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a response to the Final Action mailed September 18, 1996. Please enter the following amendments and the remarks to place this application in condition for allowance or, failing that, in better condition for appeal.

IN THE SPECIFICATION:

At the following places, please insert --M-- after "0.001": Abstract, last line, page 3, line 16, page 3, line 19, page 9, line 7, page 17, line 5.

IN THE CLAIMS:

In claim 1, step (a), line 3, replace "a given" with --an--.

In claim 1, step (b), line 2, insert the word --increased-- before "anticomplement".

In claim 10, insert --M-- after "0.001".

In claim 21, line 3, insert --M-- after "0.001".

REMARKS

RE: 35 USC 112 (vague and indefinite): The above amendments are requested to overcome the Rejection under 35 USC 112, second paragraph. No new matter is introduced. No new issues are raised. The amendments require that incubation step (b) decreases the amount of anticomplement activity (ACA) caused by step (a). The examiner objected to the use of the word "given". The amendment to step (a) removes that word. Basis for adding the word --increased-- to step (b) can be found in step (a) as amended earlier. With the above amendments the earlier objection to claims 1, 3-6, 10, 21 and 23 as being vague and indefinite should no longer be an issue.

RE: Claim 10 (ionic strength): The examiner found claim 10 vague and indefinite because it recites an ionic strength of less than 0.001 but does not define the units associated with 0.001. Although the applicant believes that the expression of ionic strength in the application as filed is proper, the applicant is requesting that the specification and claims be amended to indicate that the unit associated with ionic strength is molarity.

At page 9, lines 4-7, the applicants point out that ionic strength was determined in accordance with Perrin (see enclosed copy). Note that the ionic strength described in the Tenold patent, cited by the examiner, also uses the same unit-less method of reflecting ionic strength. See both Perrin and the enclosed copy of page 5 from a standard chemistry text, Biochemical Calculations, 1968, showing how ionic strength is conventionally expressed without units, but the reader of ordinary skill in the art would readily ascertain that the units are molarity.

RE: Claims 3-6, 21 and 23 (use of "wt./wt."): Reconsideration of the rejection of claims 3-6, 21 and 23 is requested. The examiner objected to the designation of "wt./wt." because it was unclear what the wt./wt. referred to.

It is clear from the application and examples that the invention is concerned with treating an aqueous solution of antibodies. Thus, the wt./wt. designation refers to the weight of antibodies (or protein) per unit water. Actual references to the words aqueous or water can be found in the second full paragraph on page 5. See also page 7, seventh line from the bottom. Also, it can be appreciated that the incubation step of (b) for all claims is under controlled conditions of pH and pH by definition is the negative logarithm of hydrogen ion concentration in grams/liter of water. Thus, the reference to either a 5% or 10% wt./wt. designation of the antibody solutions of claims 3-6, 21 and 23 clearly refers to the weight of antibodies per weight of water. The examiner may also refer to Fritz and Schenk, Quantitative Chemistry, p. 8 (copy enclosed) which defines weight per cent concentration as it is known in the art.

REJECTIONS UNDER 35 USC 103: Although it may have been an obvious step to combine the TNBP viral inactivation teachings of Neurath et al. with the immune globulin of Tenold, this would only result in step (a). There is no suggestion or even motivation to take the process one step further by requiring an incubation step (b) since the increase in ACA caused by using TNBP in step (a) was unexpected. A combination of the art as suggested by the examiner assumes the ACA increase was expected but there is no evidence to support that assumption.

Even if it could have been expected, it would not suggest the claims. This is particularly the case in the present invention which shows that the conditions pH, temperature and ionic strength of step (b) must be selected to reduce the ACA to an acceptable level for IV administration. As pointed out on page 9, an acceptable level of ACA will depend on the weight of protein in the solution that is being treated. There is no evidence the prior art even recognized the problem, much less the solution to the problem as described in the claims. Thus, the combination of selected portions of Tenold and Mitra with the viral inactivation of Neurath et al. and Joy Yang et al. requires the use of hindsight. This is clearly impermissible to support a rejection under 35 USC 103.

The examiner is again invited to review the revised Figure included in the earlier response. In the revised Figure (submitted only to illustrate the invention and not for purposes of being a Formal Drawing), the increased ACA observed when using the viral inactivation technique of Neurath et al. (see middle bar) was surprising. It was only by the applicant's discovery of the unexpected increase of ACA caused by step (a) that the follow up invention of step (b) was possible. In other words, if the

immune globulin of Tenold were simply combined with the viral inactivation of Neurath et al., one skilled in the art might not have even expected the rise in ACA, much less discovered a way to reduce it.

The examiner states that Tenold and Mitra et al. teach the reduction of ACA by incubation under controlled pHs, temperature, and tonicity for an extended period of time. Applicants traverse such an interpretation of these references. Tenold teaches a formulation of IgG which yields a preparation already having low ACA which is stable for at least six months. Tenold does not teach how to obtain a decrease in ACA. Moreover, Tenold describes IgG aggregation as causing ACA. In the present invention, lowering of ACA was not due to decreased IgG aggregates because these TNBP/cholate treated IGIV preparations already contained low levels of aggregated IgG (as measured by HPLC) prior to incubation.

Mitra et al. describe the antiviral action of incubation for at least 3 days at pH 4.25, low ionic strength, and 27°C. However, these authors do not disclose a lowering of IgG ACA due to such incubation conditions. Mitra et al. would not have recognized that TNBP treatment caused an increase in ACA and, by teaching a viral inactivation without chemical agents such as TNBP actually teach away from the claims.

In view of the above amendments and remarks, it is submitted that this application is now in condition for allowance and prompt allowance is requested. If the examiner has any further questions regarding the above amendments or remarks, that examiner is invited to telephone the undersigned at anytime.

PATENT
MSB-7232

Respectfully submitted,

Dated: Nov. 18, 1996

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EXHIBIT 8

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 9

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 10

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on January 3, 2007, the within document was filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following; that the document was served on the following counsel as indicated; and that the document is available for viewing and downloading from CM/ECF.

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